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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,440	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/31/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

The Preliminary Amendment, submitted 15 November 2001, and the Information Disclosure Statement, submitted 31 May, have been entered. Claims 1-118 have been cancelled. Claims 119-131 have been entered.

Claims 119-131 are under examination in the Instant Application.

Informalities

Specification

The disclosure is objected to because of the following informalities:

URL's

The disclosure is objected to because it contains browser-executable code. This occurs, for example, in paragraph 2920, for example. All URL's should be removed from the Specification. Applicant may refer to web sites by non-executable name only. See MPEP § 608.01 (p).

Appropriate correction is required.

Continuity

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: The Provisional patent applications listed in the first paragraph of the instant specification do not refer to SEQ ID NO: 351, SEQ ID NO:

350, PRO 1153, or Figure 246. Therefore, for this Office Action, the filing date of 15 November 2001 of the instant Application is considered as the priority date.

Claim Rejections/Objections

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

The following is a quotation of 35 U.S.C. 101:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-131 are rejected under 35 U.S.C. 101 because the claimed invention lacks a credible, specific and substantial asserted utility or a well-established utility.

The claims are directed to antibodies made against the polypeptide of SEQ ID NO: 351 (see Specification: Figure 246, *PRO1153* or *DNA59842-1502*). Further limiting claims are presented to monoclonal antibodies, humanized antibodies, antibody fragments, labeled antibodies, and antibodies that bind "specifically" to the polypeptide. However, the specification does not disclose a function for the antibodies against SEQ ID NO: 351, in the context of the cell or organism.

No well-established utility exists for newly isolated complex biological molecules. However, the specification asserts the following as credible, specific and substantial patentable utilities for the claimed polypeptide encoded by the claimed polynucleotide:

1) To produce the PRO1153 polypeptide and fragments.

2) To produce a variant polypeptide.

3) For use in receptor localization.

4) In assays to screen for compounds capable of modifying the interaction between receptor and ligand.

5) To make antibodies to the polypeptide encoded by the polynucleotide of SEQ ID NO: 351.

6) To detect or treat cancer.

Each of these shall be addressed in turn:

1) *To produce the PRO1153 polypeptide and fragments.* This asserted utility is credible and substantial, but not specific. Many nucleotide sequences can be used to make polypeptides. However, if the specification discloses nothing specific and substantial about the polynucleotides or polypeptides, both the polynucleotides and polypeptides produced have no patentable utility.

2) To produce a variant polypeptide. This asserted utility is credible but not substantial or specific. Such assays can be performed with any polynucleotide. Further, the specification discloses nothing specific or substantial for the variant nucleotide and polypeptide that is

produced by this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

3) For use in receptor localization. This asserted utility is credible, but it is neither substantial nor specific. Ligands and antibodies can be used to detect binding partners of the claimed polypeptide, and thus the asserted utility is not specific. Further, the specification does not disclose specific receptor targets. Since this asserted utility is not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4) In assays to screen for compounds capable of modifying the interaction between receptor and ligand. This asserted utility is also credible and substantial but not specific. Such can be performed for any receptor-ligand pair. Additionally, the specification discloses nothing specific or substantial for the compounds that can be identified by this method.

5) To make antibodies to the polypeptide encoded by the polynucleotide of SEQ ID NO: 351. This asserted utility is credible and substantial, but not specific. Antibodies can be made to any polypeptide. However, if the specification discloses nothing specific and substantial about the polypeptide, the polypeptide, the polynucleotide encoding the polypeptide and antibodies have no patentable utility.

6) To detect or treat cancer. Table 9B of the instant Specification sets forth the results of assays to determine the number of clone copies in a variety of tissues. A ΔCt of >1 was typically used as the threshold value for amplification scoring, as this represents a doubling of gene copy. The ΔCt values indicate that significant amplification of nucleic acid DNA59842-1502 encoding PRO1153 occurred in several epithelial tumors; The Specification implies that

antagonists (e.g., antibodies) directed against the protein encoded by DNA59842-1502 (PRO1153) would be expected to have utility in cancer therapy.

However, a slight increase in clone copies in several tumor types is not indicative of a specific or substantial utility for PRO1153 for use as an agent to treat cancer. A slight increase in clone numbers in a cancerous tissue is no doubt due to an increased number of chromosomes, a very common characteristic of cancerous and non-cancerous epithelial cells (see, for example: Hittelman, W., 2001, Ann. NY. Acad. Sci., 952: 1-12, especially pages 8 and 9, and; Crowell, et al, 1996, Cancer Epidemiol. 5: 631-637), not because PRO1153 plays a significant role in tumor formation or growth. The asserted utility is therefore not specific. Experiments confirming the specificity and substantial utility of PRO1153 in terms of mRNA and protein expression were not performed. Antibodies against PRO1153 were not administered to animals to test their anti-cancer effects. Significant further experimentation would be required of the skilled artisan to determine whether PRO1153 is expressed in certain cancers to the extent that antagonists (e.g., antibodies) directed against the protein encoded by DNA59842-1502 (PRO1153) would be expected to have utility in cancer therapy. Thus, the asserted utility is not substantial. In addition, the Specification shows that gene copy number is increased in certain tumor tissue samples. However, it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased protein expression, such that the antibodies would be useful diagnostically or as a target for cancer drug development. For Example, Pennica et al (1998, PNAS 95: 14717-14722) disclose that:

"An analysis of WISP-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression

of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient," (page 14721, second paragraph).

Furthermore, although the specification teaches that PRO1153 is expressed in several epithelial cancers (Table 9B), the state of the art is such that protein expression levels cannot be accurately predicted from the level of corresponding mRNA transcript, and therefore cannot be correlated to antibody binding. Haynes et al, for example, studied 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript levels (Haynes et al., 1998, Electrophoresis 19:1862-1872). That research group found that for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold (pg 1863, paragraph 2, Figure 1). Therefore, one skilled in the art cannot predict that the PRO1153 mRNA transcript levels determined in various cancerous tissues are indicative of PRO1153 polypeptide expression in cancerous cells. Undue experimentation is required by the skilled artisan to detect and quantify PRO1153 polypeptide expression in all possible tumor tissues/cells, other than lung or epithelial cancer.

Claims 119-124 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Thus, because the polypeptide of SEQ ID NO: 351 has not been shown to be useful, antibodies made against the polypeptide also have no specific use. Applicants have implied that the PRO1153 polypeptide is a secreted protein, which possesses amino acid sequence identity with protein *HPBRII-7* (Fleischhauer, K., 1995, Accession No.

CAA47751). However, the polypeptide of SEQ ID NO: 351 bears low (20-28%) sequence identity to the polypeptide *HPBRII-7*, which itself does not have a specific function.

Applicants have implied that the PRO1153 polypeptide is a secreted protein (paragraph 4252) that can be used to bind lectins. Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-119) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:1198-1200) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p.1199). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Examples from the secreted polypeptide art demonstrate, in some cases, polypeptides with high homology having a wide-variety of functions in organisms (see Hesselgesser, et al, 1997, Methods in Enzymology, 287: 59-69, see pages 59 and 64-66) and in other cases, many different possible structures for secreted proteins that are considered related as to function (Blease, et al, 2000, Resp. Res., 1(1): 54-61). However, Applicants have not associated the disclosed PRO1153 polypeptide with any type or genus of secreted peptide.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed antibodies against PRO1153 without resorting to undue experimentation to determine what the specific biological activities of the PRO1153 polypeptide are.

The specification does not teach the skilled artisan how to use the claimed antibodies directed to the polypeptide of SEQ ID NO: 351 for any purpose. For example, there is no disclosure of particular disease states correlating to an alteration in levels or forms of the polypeptide such that the claimed antibody could be used as a diagnostic tool. The skilled artisan is not provided with sufficient guidance to use the claimed antibodies for any purpose.

Furthermore, the specification does not reasonably provide enablement for all *variants* of the PRO1153 polypeptide. The disclosure does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The specification discloses the peptide of SEQ ID NO: 351. Claims 119, 120, 130 and 131 recite variant, fused, or chimeric polypeptides in which the peptide of SEQ ID NO 351 is modified. However, the specific activities of the protein of SEQ ID NO: 351, and assays to test for its activity, are not disclosed. There is no discussion, or working examples disclosed in the instant case, as to what amino acids are necessary to maintain the functional characteristics of the claimed PRO1153 polypeptides. The instant case claims altering much of the claimed

polypeptide. However, the art shows that receptor families have members with high structural similarities but disparate functions. For example, Smith et al. (1997, Nature Biotechnology 15:1222-1223) demonstrate that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Therefore, it is not predictable as to which amino acids are necessary to maintain the functional characteristics of a protein.

Due to the large quantity of experimentation necessary to determine an activity or property of the claimed polypeptide such that it can be determined how to use the polypeptide of SEQ ID NO: 351 and to screen for activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, and the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite particular biological activities, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, first paragraph – Written Description.

Claims 119-131 are also rejected under 35 U.S.C. 112, first paragraph, as not complying with the enablement requirement. The claims are directed to a polypeptide of 197 amino acids (see Figure 246). Further claim limitations are presented to isolated polypeptides having at least 80-99% sequence identity to the polypeptide of SEQ ID NO: 351, chimeric polypeptides based on SEQ ID NO: 351, and the polypeptide of SEQ ID NO: 351 lacking its associated signal peptide. However, the specification does not disclose a function for the polypeptide of SEQ ID NO: 351 in the context of the cell or organism.

The specification teaches a polypeptide (SEQ ID NO: 351). However, the specification does not teach functional or structural characteristics of all claimed polypeptides. The description of one PRO polypeptide (SEQ ID NO: 351) is not adequate written description of an entire genus of functionally equivalent polypeptides.

To provide evidence of enablement of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of all claimed and encompassed PRO polypeptides, and therefore, would not know how to use them. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of use. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of use. The product itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 351 and a polypeptide comprising the amino acid sequence of SEQ ID NO: 351, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 USC § 112, first paragraph – Deposit Rules

Claims 119-124 and 129-131 are also rejected under 35 U.S.C. § 112, first paragraph, as not complying with the enablement requirement. The invention appears to employ novel nucleic acid molecules. Since the nucleic acid molecules are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the nucleic acid molecules are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the nucleic acid molecules. The Specification at paragraph 4515 indicates that the deposit was made under the Budapest treaty. However, Applicants have failed to provide a copy of the deposit receipt. If a deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific nucleic acid molecules have been deposited under the Budapest Treaty and that the nucleic acid molecules will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If a deposit is not made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and

(e) the deposit will be replaced if it should ever become inviable. Applicant's attention is directed to M.P.E.P. §21200 in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination. Finally, Applicant is advised that the address for the ATCC has recently changed, and that the new address should appear in the specification.

The new address is:

American Type Culture Collection
10801 University Boulevard
Manassas, VA 20110-2209

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 119-131 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 119-131 are rendered indefinite because of the phrase "extracellular domain." The metes and bounds of Claims 119-131 are indefinite in view of the instant Specification which implies and states that the polypeptide encoded by the claimed polynucleotide(s) is a secreted protein. Such an "extracellular domain" would be found in a cleaved transmembrane protein, for example, along with an intracellular domain, but is not recognized in secreted proteins since they are entirely "extracellular." In addition, extracellular domains are not normally associated with signal peptides. Thus, the recitation in the claims of an "extracellular domain [ ] lacking its associated signal peptide" is indefinite (see Claim 119, part (d), for example).

Conclusion: Claims 119-131 are rejected for the reasons recited above.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (571) 272-0887.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9252 (toll-free).

SLW

3/21/04

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER